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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/413,110	UNGER, EVAN C.	
	Examin r	Art Unit	
	Shahnam Sharareh	1619	

-- The MAILING DATE of this communication appears on the cover sheet with the correspond nce address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 May 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *116-184* is/are pending in the application. 167

4a) Of the above claim(s) *132-137, 142-145, 152-159, 161-163 and 175-177* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *116-131, 138-141, 146-151, 160, 164, 168-174, 178-184* is/are rejected. 166 SS

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15)☐ Notice of References Cited (PTO-892)

16)☒ Notice of Draftsperson's Patent Drawing Review (PTO-948) See Paper No. 7

17)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *15, 16, 19* .

18)☐ Interview Summary (PTO-413) Paper No(s). _____ .

19)☐ Notice of Informal Patent Application (PTO-152)

20)☐ Other:

DETAILED ACTION

Continued Prosecution Application

1. The request filed on January 24, 2001 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/413,110 is acceptable and a CPA has been established. An action on the CPA follows.

Status of the Claims

2. Applicant's election of perfluorobutane as the gas or gaseous precursor, thrombolytic agent as the bioactive agent, phospholipids as a component of the vesicles, and an area of reduced blood perfusion as the target tissues at the flushing rate of 1 x 10^{6} to about 8 x 10^{6} vescicles / Kg-sec, in Paper No. 18 is acknowledged. Claims 116-131, 138-141, 146-151, 160,164-166, 168-174, and 178-184 are directed to the elected species.

Accordingly, claims 132-137, 142-145, 152-159, 161-163, 167 175-177 are withdrawn from further consideration by the Examiner, because they are directed to non-elected species.

This application contains claims drawn to an invention nonelected without traverse in Paper No. 18. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP 821.01.

Priority

3. The effective priority date used for the examination of the instant application is October 6, 1999, because none of the parent cases teaches methods for enhancing

bioavailability of bioactive agents such as genetic agents including hammerhead RNA (claims 160,163) or an angiogenic agent (claim 160) comprising steps administering the bioactive agent to a patient, administering a vescilce contatining composition at a continous infusion rate and then applying ultrasound.

Double Patenting

4. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 116-131, 138-141, 146-151, 160,164, 168-174, and 178-184 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over patented claims of U.S. Patent No. 6,143,276, 6,123,923, 5,770,222, 5,580575. Although the conflicting claims are not identical, they are not patentably distinct from each other because they are all directed to methods of delivering a bioactive agent in combination with a gaseous liposomal composition and then applying an ultrasounic energy source (see for example claim 24 of US Patent 6,123,923 or claim 16 of US Patent 5,58,0575).

Claim116-131, 138-141, 146-151, 160,164, 168-174, and 178-184 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over the pending claims of copending Application No. 09/218,660. Although the conflicting claims are not identical, they are not patentably distinct from each other because methods of delivering a bioactive agent comprising a therapeutic agent, a gaseous composition to a site of interest, and then applying ultrasonic energy.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 116-131, 138-141, 146-151, 160,164-166, 168-174, and 178-184 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 116 and 164, the phrase the "enhancing the delivery of a bioactive agent in tissue" is ambiguous. It is not clear what is the metes and bounds of the intended enhancment. What is the basis of the enhancement? The specification is silent about the degree of enhancing the delivery. In addition what is the basis of comparison between the actual delivery of the bioactive and the instant claimed enhancement. The

claims appear to be drafted in the form of a Jepson type claim without clarifying what the actual improvement is. Accordingly, the metes and bounds of the claims are not clear.

In claims 116 and 164, the recitation of "at a rate which comprises continuous infusion" is ambiguous." It is not clear what is meant by this recitation? More specifically it appears to be in an improper Markush language. Is applicant referring to a rate that is continuous or it can be continous? It appears that the transitional language "comprising" renders the scope of the claim indefinite.

Claim Rejections - 35 USC 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 116-131, 138-140, 160,164-166, 168-174, and 178-184 rejected under 35 U.S.C. 102(b) as being anticipated by Siegel US Patent 5,695,460.

The instant claims are now directed to methods of enhancing bioavilability and delivery of a bioactive agent comprising (I) administering an agent to a patient, (ii) administering a vesicle composition comprising an aqueous carrier, a gas or gaseous precursor, and vesicles comprising lipids, proteins or polymers to the patient (iii) and applying ultrasonic energy to a tissue, wherein the gas comprise a perfluorocarbon, and the tissue is a reduced perfusion tissue.

Siegel et al disclose methods of utilizing an ultrasonic energy and an ultrasonic contrast agent containing perfluorinated microbubbles in combination with a thrombolytic agent to treat vascular thrombosis, (abstract; col 2 lines 1-65; examples 1-5; col 14, lines 4-30). Siegel specifically disclose that the ultrasound may be applied intravascularly by means of a miniature ultrasonic transducer or by a guide wire for transmitting ultrasound directly into the vessel (col 2, lines 7-10). Siegel's preferred ultrasound contrast agent is Echogen which contains phospholipids and polyethylene glycol (col 5, lines 50-53). Siegel et al further indicate the use of other types of contrast agents such as gas filled liposomes, or gas filled microbubble for their thrombus lysing method (col 5, lines 30-48). Siegel administers his drugs to an area in proximity of a thrombosis, which by its nature is hypo-perfused. Accordingly, Siegel et al meet the limitations set forth in the instant claims.

Claim Rejections - 35 USC 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 116-131, 138-141, 146-151, 160,164, 168-174, and 178-184 are rejected under 35 U.S.C. 103(a) as being unpatentable over Porter TR et al (Am Heart J 1996 Nov 132(5):964-968 abstract.) in view of Porter US Patent 5,648,098, and further in view of Schutt et al US Patent 5,626,833.

The instant claims are directed to methods of lysing a thrombus comprising (I) administering a thrombolytic agent to a patient, (ii) administering a vesicle composition comprising an aqueous carrier, a gas or gaseous precursor, and vesicles comprising lipids, proteins or polymers to the patient (iii) and applying ultrasonic energy to the thrombus area, wherein the gas comprise a perfluorocarbon, and the thrombus is in a cardiac blood vessel.

Porter et al disclose a method of treating thrombosis comprising administering aqueous solution of dextrose 5% containing microbubbles comprising a polymeric wall made of albumin, and perfluorocarbon gas, (ii) administering a thrombolytic agent such as urokinase, (iii) and applying ultrasound simultaneously to achieve better thrombolysis (see abstract). Formation of a thrombous by its nature results in decrease perfusion in the sourrounding tissue, Thus, Porter's method is directed to a reduced perfusion tissue. Accordingly, Porter teaches methods of administering gaseous microbubbles to improve the thrombolytic activity of agents and thus its bioavilability in a hypo- perfused tissue.

Porter in US Patent 5,648,098 also teaches the effective use of perfluorocarbonated microbubbles alone at a rate of 0.0025-1ml/kg over about 1-25 minutes (which is roughly about 1.6×10^{-6} to 6×10^{-6} ml-kg/sec), wherein perfluorocarbon gas is perfluorobutane (see claims 1-5) and wherein the microbubble concentration was less than 0.8×10^{9} or greater than $1.5\ 10^{9}$ per each milliliter (col 6, line33-36). Thus, allowing an artisan to accurately measure the dose of the

microbubbles during the infusion. However, Porter fails in both of his teachings disclose vesicles comprising phospholipids.

Schutt et al disclose various types of perfluorinated microbubbles for use as ultrasound contrast agent comprising phospholipid containing walls (see claims 1-10). Schutt et al further indicate that the use of their perfluorocarbon containing compositions can enhance the thrombolytic activity of agent such as TPA or Streptokinase (see col 11, lines 18-30).

The teachings of Porter and Schutt are viewed as being in the same field of endeavor because they all teach the enhancement of thrombolytic activity when administering perfluorinated microbubbles.

The policy of the US PTO is to give pending claims their broadest reasonable interpretation. The instant open-ended claims comprise and do not exclude any components or method steps essential to the operability of the cited prior arts. Furthermore, differences in ranges will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such ranges (such as the instant rate of administration) is critical. Where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.

It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose. "the idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven*, 626 F.2d 846, 205

USPQ 1069, 1072 (CCPA 1980) (citations omitted). Therefore, one ordinary skilled in the art would have been motivated at the time of invention to combine the teachings of Porter et al (Am Heart J abstract) and Porter US Patent 5,648,098, because he would have had a reasonable expectation of success in enhancing the lytic effects of thrombolytics such as streptomycin in treatment of thrombosis. Further, it is well within purview of an ordinary skilled artisan to optimize the rates of administration of the contrast agents that are disclosed by Porter in US Patent 5,648,098, and establish administration rates for the contrast agents of choice. Finally, modifying Porter□s compositions as taught by Schutt and formulating phospholipid containing microbubbles to be used in Porter's method, would have also been obvious.

8. Claims 141, 146-151 rejected under 35 U.S.C. 103(a) as being unpatentable over Siegel et al US Patent 5,695,460.

The teachings of Siegel et al are described above.

Although Siegel et al do not specifically teach various infusion rates or various types of liposomal entities as the instant claimed invention, he does indicate the use of various types of contrast agents such as gaseous liposomes in this methods, accordingly, it would have been obvious to one of ordinary skill in the art to use a perfluorinated liposomal entity known in the art and further determine its suitable rate of infusion by routine experimentation, because he would have had a reasonable expectation to succeed in enhancing the lysis of a vessel thrombus when utilizing a gas filled liposomal contrast agents. Moreover, changes in rate of administration will not support the patentability of subject matter encompassed by the prior art unless there is

evidence indicating such rate of administration is critical. Where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.

9. Claims 116-131, 138-141, 146-151, 160,164-166, 168-174, and 178-184 rejected under 35 U.S.C. 103(a) as being unpatentable over Porter US Patent 5,648,098 in view of Siegel et al US Patent 5,695,460.

The teachings of Porter, and Siegel are previously described. Porter, Siegel and Schutt are viewed as being in the same field of endeavor because they all teach the enhancement of thrombolytic activity when administering perfluorinated microbubbles.

Although Porter does not teach a liposomal entity as a gaseous composition in his methods, one ordinary skilled in the art would have been motivated at the time of invention to use liposomes as taught by Siegel instead of protein shells of Porter, because an ordinary practitioner would have had a reasonable expectation to succeed in observing similar results as Porter when using the liposomes described by Siegel. Further, it is well within purview of an ordinary skilled artisan to optimize and determine the suitable rates for administration of the contrast agents that are disclosed by Porter.

Conclusion

10. No claims are allowed. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shahnam Sharareh, PharmD whose telephone number is (703) 306-5400. The examiner can normally be reached on Monday to Friday from 8:30 a.m. to 5:00 p.m. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Diana Dudash can be reached

on 703-308-2328. The fax phone number for this Group is 703-308-4556. Any inquiry of a general nature of relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is 703-308-1235.

sjs 7/12/01